



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 5 :</b> <b>A61K 9/16, 9/00</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/17667</b> <b>(43) International Publication Date:</b> 16 September 1993 (16.09.93)
<b>(21) International Application Number:</b>	PCT/JP93/00291	<b>(74) Agent:</b>	KITAGAWA, Tomizo; Patent Division, Taisho Pharmaceutical Co., Ltd., 24-1, Takata 3-chome, Toshima-ku, Tokyo 171 (JP).
<b>(22) International Filing Date:</b>	10 March 1993 (10.03.93)	<b>(81) Designated States:</b>	AU, BR, CA, FI, KR, NO, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
<b>(30) Priority data:</b> 4/53442 12 March 1992 (12.03.92) JP 4/219904 19 August 1992 (19.08.92) JP		<b>Published</b>	<i>With international search report.</i>
<b>(71) Applicant (for all designated States except US):</b> TAISHO PHARMACEUTICAL CO., LTD. [JP/JP]; 24-1, Takata 3-chome, Toshima-ku, Tokyo 171 (JP).			
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> YAJIMA, Toshio [JP/JP]; ISHII, Kuniaki [JP/JP]; UMEKI, Nobuo [JP/JP]; ITAI, Shigeru [JP/JP]; HAYASHI, Hidefumi [JP/JP]; SHIMANO, Kimihide [JP/JP]; KOYAMA, Ikuo [JP/JP]; Taisho Pharmaceutical Co., Ltd., 24-1, Takata 3-chome, Toshima-ku, Tokyo 171 (JP).			

**(54) Title:** COMPOSITION FOR ORAL PREPARATIONS**(57) Abstract**

There are provided a composition for oral preparations, which comprises a complex formed by dispersing or dissolving an unpleasantly tasting basic drug and a function polymer compound in a substance having a low melting point, 10 to 70 % by weight, based on the composition, of sugaralcohol and 0.1 to 7 % by weight, based on the composition, of basic oxide. The composition for oral preparation is excellent in masking unpleasantly tasting basic drugs and has excellent performance in biological use.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	MI	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam

## DESCRIPTION

## COMPOSITION FOR ORAL PREPARATIONS

## TECHNICAL FIELD

The present invention relates to a composition for preparations of basic drugs which taste unpleasant. More specifically, it relates to a composition for oral preparations, which is excellent in masking unpleasantly tasting basic drugs and has excellent performance in biological use.

## BACKGROUND ART

There have been hitherto found a variety of methods for masking the tastes of unpleasantly tasting drugs. For example, JP-A-49-81526 discloses a method in which macrolide is dissolved in an inert volatile organic solvent in which a coating polymer selected from the group consisting of polyvinylacetal diethylaminoacetate (hereinafter abbreviated as AEA), cellulose acetate dibutylaminohydroxypropyl ether, Eudragit® E and ethyl cellulose and at least one member selected from the group consisting of wax, higher fatty acid and salt insoluble in higher fatty acid have been dissolved or dispersed, the resultant solution is spray-dried to form coated macrolide particles, and the coated macrolides particles are recovered.

Further, as a pharmaceutical mixture for masking the taste of unpleasantly tasting basic drugs, for example, U.S. Patent 4,656,027 disclose a dry powder for use as a pharmaceutical preparation, which dry powder is prepared by

mixing a pharmaceutically acceptable basic substance with a bad tasting pharmaceutical which is in a form insoluble at high pH and encapsulating the mixture.

U.S. Patent 4,994,260 discloses a pharmaceutical preparation for controlled release of a pharmaceutically active substance, which masks bad taste and increases stability of the pharmaceutically active substance and contains an encapsulated active substance in combination with 60 to 99 % by weight of a release-controlling substance selected from the group consisting of polysaccharides, oligosaccharides, disaccharides, monosaccharides, polyhydroxy alcohols and mixtures thereof.

For dissolving a conventional coating agent, however, there is used an organic solvent such as methylene chloride, chloroform, cyclohexane, carbon tetrachloride, methyl ethyl ketone, acetone, methyl alcohol or isopropyl alcohol. It is therefore required to carry out a drying step for removing the solvent. As a result, the coating is porous, and that the drying step extraordinarily requires time, facilities, labor and cost. Further, this step involves risks of ignition and explosion, and moreover, a product might contain a residual solvent to have a detrimental effect on a human body.

#### DISCLOSURE OF INVENTION

The present inventors have made an initial study on the masking of taste for overcoming the above-described problems.

At first, a study has been made of the selection of a material. As the material, which is excellent in forming a

dense coating is concerned, a substance having a low melting point (wax) is available. Further, as far as a material which is readily soluble at low pH (pH 1 - 4, endogastric pH) and which is insoluble or hardly soluble in the mouth (pH 5 - 8) is concerned, a functional polymer may be taken into consideration. However, an organic solvent is required for dissolving the functional polymer, and there might be a risk concerning the toxicity and handling of the solvent. Further, since the functional polymer forms a porous coating or cannot form a dense coating, it is difficult to mask unpleasant taste sufficiently.

Therefore, studies have been made, and it has been found that, without any organic solvent, a functional polymer can be dissolved or dispersed in a substance having a low melting point when the substance having a low melting point has been melted. It has been also found that the resultant solution or dispersion of the functional polymer is cooled to give a dense coating and that the working can be carried out safely.

Additives for enhancing the masking effect have been studied. Usual additives such as carbonates, phosphates, citrates and hydroxides cannot be said to maintain sufficient masking of taste, while specific basic oxides, particularly magnesium oxide, have an excellent effect.

It has been also found that the masking for unpleasantly tasting basic drugs is insufficient when sugar is added as an additive.

As a result, the present inventors have found a composition for preparations of unpleasantly tasting basic drugs which maintains the masking of the taste of

unpleasantly tasting basic drug and has excellent bioavailability and a process for the preparation thereof, the composition being obtained by melting a substance having a low melting point under heat at a temperature equal to or higher than the melting point thereof, dispersing or dissolving a functional polymer compound in the resultant molten substance to form a composition, melt- or heat-granulating the composition and an unpleasantly tasting basic drug to form a complex and incorporating sugaralcohol and basic oxide into the complex.

That is, the present invention provides a composition for oral preparations, which comprises a complex formed by dispersing or dissolving an unpleasantly tasting basic drug and a functional polymer compound in a substance having a low melting point, 10 to 70 % by weight, based on the composition, of sugaralcohol and 0.1 to 7 % by weight, based on the composition, of basic oxide.

In the present invention, the unpleasantly tasting basic drug includes unpleasantly tasting macrolides such as erythromycin, clarithromycin, kitasamycin, josamycin, midecamycin, roxithromycin and azithromycin. The amount of the unpleasantly tasting drug in the complex is 1 to 90 % by weight, preferably 1 to 60 % by weight.

The functional polymer compound used in the present invention includes Eudragit<sup>R</sup> E, AEA and a mixture of these.

The substance having a low melting point, used in the present invention, refers to a water-insoluble or water sparingly soluble substance having a pharmaceutically acceptable melting point of 40 to 120 °C, and includes paraffin, microcrystalline wax, ceresine, hydrogenated oil,

- 5 -

haze wax, cacao butter, myristic acid, palmitic acid, stearic acid, cetanol, stearyl alcohol, macrogol 6000, macrogol 4000, carnauba wax, bees wax, D-glucose, D-sorbitol, titanium stearate, calcium oleate, glycerin fatty acid ester, propylene glycol fatty acid ester, sorbitan fatty acid ester and mixtures of these. Preferred are glycerin monostearate, steary alcohol, stearic acid and mixtures of these.

The amount of the functional polymer compound in the complex is 1 to 60 % by weight, particularly preferably 2 to 40 % by weight. The amount of the complex in the composition for oral preparations is 20 to 60 % by weight, preferably 30 to 50 % by weight.

The sugaralcohol used in the present invention includes sorbitol, xylitol, mannitol, maltitol and mixtures of these. Preferred are sorbitol, mannitol, xylitol and mixtures of these.

The amount of the sugaralcohol used in the present invention based on the composition for oral preparations is 10 to 70 % by weight, preferably 30 to 65 % by weight.

The basic oxide used in the present invention includes magnesium oxide and aluminum oxide. Preferred is magnesium oxide. The amount of the basic oxide based on the composition for oral preparations is 0.1 to 7 % by weight, preferably 0.1 to 2 % by weight. The dose of magnesium oxide is not more than 70 mg.

In producing the composition for oral preparations, provided by the present invention, the complex is first produced by a so-called melt-granulation method or heat-granulation method. For example, the complex can be

produced by dispersing or dissolving a functional polymer compound in a substance having a low melting point which is heated to a temperature equal to or higher than its melting point, mixing a unpleasantly tasting basic drug with the resultant dispersion or solution at a high temperature and cooling the mixture.

Then, the composition for oral preparations, provided by the present invention, is obtained by adding and mixing a sugaralcohol and a basic oxide to the above-obtained complex. The mixing may be carried out by a general granulating method such as fluidized bed granulation or agitating granulation. In the granulation, a solution or suspension of the basic oxide in water or a binder solution is used as a solvent for the fluidized bed granulation or agitating granulation, whereby there can be obtained a desirable composition for oral preparations. That is, the composition gives preparations in which the drug is hardly eluted from the complex.

The so-obtainable composition for oral preparations can be formed into solid oral preparations such as granules, a powder, a capsule, a tablet and dry syrup by optionally mixing it with other known additives such as an excipient, a disintegrant, a binder, a lubricant, an antioxidant, a coating agent, a colorant, a flavor, a surfactant and a plasticizer.

The excipient includes crystalline cellulose, sodium carboxymethyl cellulose, calcium hydrogenphosphate, flour starch, rice starch, corn starch, potato starch, sodium carboxymethyl starch, dextrin,  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, carboxyvinyl polymer, light silicic acid

anhydride, titanium oxide, magnesium aluminomethasilicate, polyethylene glycol and medium chain triglyceride.

The disintegrant includes hydroxypropyl cellulose substituted in a low degree, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (Ac-Di-sol<sup>®</sup>), starch, crystalline cellulose, hydroxypropyl starch and partially alpha-formed starch.

The binder includes methyl cellulose, hydroxypropyl cellulose, hydroxylpropylmethyl cellulose, polyvinyl pyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan,  $\alpha$ -starch, agar, tragant, sodium alginate, and propylene glycol alginate ester.

The lubricant includes magnesium stearate, calcium stearate, polyoxyl stearate, cetanol, talc, hydrogenated oil, sucrose fatty acid ester, dimethyl polysiloxane, microcrystalline wax, bees wax and white beeswax.

The antioxidant includes dibutylhydroxytoluene (BHT), propyl gallate, butylhydroxyanisole (BHA),  $\alpha$ -tocopherol and citric acid.

The coating agent includes hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylcellulose, acetate phthalate cellulose, polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer, hydroxypropylmethyl cellulose acetate succinate, a methacrylic acid copolymer, cellulose acetate trimellitate (CAT), polyvinyl acetate phthalate and shellac.

The colorant includes tar dyestuff and titanium oxide.

The surfactant includes polyoxyethylene hardened castor oil, glycerin monostearate, sorbitan monostearate, sorbitan monoplamicate, sorbitan monolaurate, a polyoxyethylene polyoxypropylene block copolymer, polysorbates, sodium laurylsulfate, macrogols and sucrose fatty acid ester.

The plasticizer includes triethyl citrate, triacetin and cetanol.

The flavor includes menthol.

#### INDUSTRIAL APPLICABILITY

The composition for oral preparations, provided by the present invention, constantly masks the taste of unpleasantly tasting basic drugs and is excellent in bioavailability.

Further, the composition for oral preparations of unpleasantly tasting basic drugs, provided by the present invention, does not give unpleasant taste when suspended in water and further continuously stored at 5 °C for 3 days. Moreover, the composition of the present invention is excellent in bioavailability and gives excellent preparations as oral preparations such as syrup for infants.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention will be specifically explained hereinafter by reference to Examples and Text Examples.

##### Example 1

700 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved

therein. Further, 200 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 20 % clarithromycin complex was obtained. 90 Grams of sorbitol, 0.2 g of magnesium oxide and 9.8 g of crystalline cellulose were added to 100 g of the above complex to give a composition containing 10 % of clarithromycin for oral preparations.

### Example 2

600 Grams of stearic acid was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % clarithromycin complex was obtained. 100 Grams of sorbitol, 100 g of xylitol, 347 g of mannitol, 50 g of maltitol and 70 g of magnesium oxide were added to 333 g of the above complex to give a composition containing 10 % of clarithromycin for oral preparations.

### Example 3

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet

- 10 -

temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % clarithromycin complex was obtained. 657 Grams of sorbitol and 10 g of magnesium oxide were added to 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation with water to give a composition containing 10 % of clarithromycin for oral preparations.

#### Example 4

600 Grams of glycetyl monostearate was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % clarithromycin complex was obtained. 500 Grams of mannitol, 20 g of magnesium oxide, 125 g of starch, 20 g of hydroxypropyl cellulose and 2 g of carboxymethyl cellulose were added to, and homogeneously mixed with, 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation with water to give a composition containing 10 % of clarithromycin for oral preparations.

#### Example 5

600 Grams of hydrogenated oil was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet

- 11 -

temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % clarithromycin complex was obtained. 300 Grams of sorbitol, 300 g of mannitol, 10 g of sodium carboxymethyl cellulose and 47 g of crystalline cellulose were added to 333 g of the above complex. Separately, 10 g of magnesium oxide was suspended in water to prepare a binder solvent. The above-obtained mixture was subjected to fluidized granulation in the presence of the binder solvent to give a composition containing 10 % of clarithromycin for oral preparations.

#### Example 6

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % clarithromycin complex was obtained. 300 Grams of sorbitol, 100 g of mannitol, 100 g of xylitol, 100 g of maltitol, 10 g of sodium carboxylethyl cellulose, 20 g of magnesium oxide, 14 g of starch, 20 g of hydroxypropyl cellulose and 3 g of saccharin sodium were added to, and homogeneously mixed with, 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a dry syrup-containing 10 % of clarithromycin.

#### Example 7

- 12 -

600 Grams of glycetyl monostearate was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % clarithromycin complex was obtained. 400 Grams of sorbitol, 229 g of xylitol, 10 g of sodium carboxymethyl cellulose, 5 g of magnesium oxide, 20 g of hydroxypropyl cellulose and 3 g of saccharin sodium were added to, and homogeneously mixed with, 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of clarithromycin for oral preparations.

One gram of the above-obtained composition was suspended in about 5 ml of water to give a syrup.

#### Example 8

700 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 200 g of erythromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 20 % erythromycin complex was obtained. 90 Grams of sorbitol, 0.2 g magnesium oxide and 9.8 g of crystalline cellulose were added to 100 g of the above complex to give a composition containing 10 % of erythromycin for oral preparations.

**Example 9**

600 Grams of stearic acid was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved herein. Further, 300 g of erythromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % erythromycin complex was obtained. 100 Grams of sorbitol, 100 g of xylitol, 347 g of mannitol, 50 g of maltitol and 70 g of magnesium oxide were added to 333 g of the above complex to give a composition containing 10 % erythromycin for oral preparations.

**Example 10**

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % erythromycin complex was obtained. 657 Grams of sorbitol and 10 g of magnesium oxide were added to 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation with water to give a composition containing 10 % of erythromycin for oral preparations.

**Example 11**

600 Grams of hydrogenated oil was melted at about 100

'C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % erythromycin complex was obtained. 300 Grams of sorbitol, 300 g of mannitol, 10 g of sodium carboxymethyl cellulose and 47 g of crystalline cellulose were added to 333 g of the above complex. Separately, 10 g of magnesium oxide was suspended in water to prepare a binder solvent. The above-obtained mixture was subjected to fluidized granulation in the presence of the binder solvent to give a composition containing 10 % of erythromycin for oral preparations.

#### Example 12

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % erythromycin complex was obtained. 300 Grams of sorbitol, 100 g of mannitol, 100 g of xylitol, 100 g of maltitol, 10 g of sodium carboxymethyl cellulose, 20 g of magnesium oxide, 14 g of starch, 20 g of hydroxypropyl cellulose and 3 g of saccharin sodium were added to, and homogeneously mixed with, 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation in the presence of

water as a granulating solvent to give a dry syrup-containing 10 % of erythromycin.

### Example 13

600 Grams of glycenyl monostearate was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was dispersed in the mixture. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm. As a result, about 950 g of a 30 % erythromycin complex was obtained. 400 Grams of sorbitol, 229 g of xylitol, 10 g of sodium carboxylmethyl cellulose, 5 g of magnesium oxide, 20 g of hydroxypropyl cellulose and 3 g of saccharin sodium were added to, and homogeneously mixed with, 333 g of the above complex, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of erythromycin for oral preparations.

One gram of the above-obtained composition was suspended in above 5 ml of water to give a syrup.

### Test Example 1

#### (Test compositions)

Composition for oral preparations, prepared in Example 3.

Compositions for oral preparations, prepared in the same manner as in Example 3 except that the magnesium oxide was replaced with the same amount of sodium hydrogencarbonate, magnesium carbonate, magnesium hydroxide,

- 16 -

sodium dihydrogenphosphate or Neucilin®.

(Test method)

One gram of each of the test compositions was orally administered to 10 healthy adults to evaluate the bitterness of each composition. The evaluation was conducted on the basis of the following six ratings immediately after administration until 10 minutes passed.

- 0: Taste no bitterness
- 1: Taste a presence of bitterness
- 2: Taste bitter to some extent
- 3: Taste bitter
- 4: Taste bitter, but tolerable
- 5: Taste bitter intolerably

(Results)

The evaluation results on each test composition by the ten adults were average, and Fig. 1 shows the results.

### Test Example 2

(Test compositions)

Compositions for oral preparations, prepared in Examples 1 to 13.

Compositions prepared as described in the following Control Examples 1 to 10.

### Control Example 1

700 Grams of stearyl alcohol was melted at about 100 °C, and 300 g of clarithromycin was dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950

g of a 30 % clarithromycin composition.

#### Control Example 2

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % clarithromycin composition.

#### Control Example 3

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % clarithromycin composition. Then, 657 g of sorbitol and 10 g of crystalline cellulose were added to, and homogeneously mixed with, 333 g of the above-obtained composition, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of clarithromycin.

#### Control Example 4

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved

therein. Further, 300 g of clarithromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % clarithromycin composition. Then, 70 g of magnesium oxide and 667 g of crystalline cellulose were added to, and homogeneously mixed with, 333 g of the above-obtained composition, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of clarithromycin.

#### Control Example 5

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % clarithromycin composition. Then, 70 g of magnesium oxide, 5 g of sorbitol and 592 g of crystalline cellulose were added to, and homogeneously mixed with, 333 g of the above-obtained composition, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of clarithromycin.

#### Control Example 6

600 Grams of stearyl alcohol was melted at about 100 °C,

and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of clarithromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % clarithromycin composition. Then, 100 g of magnesium oxide and 567 g of sorbitol were added to, and homogeneously mixed with, 333 g of the above-obtained composition, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of clarithromycin.

#### Control Example 7

700 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % erythromycin composition.

#### Control Example 8

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % erythromycin composition.

### Control Example 9

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % erythromycin composition. Then, 657 g of sorbitol and 10 g of crystalline cellulose were added to, and homogeneously mixed with, 333 g of the above-obtained composition, and the resultant mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % erythromycin.

### Control Example 10

600 Grams of stearyl alcohol was melted at about 100 °C, and 100 g of Eudragit® E was dispersed and dissolved therein. Further, 300 g of erythromycin was also dispersed therein. The resultant dispersion was spray-cooled and granulated with a spray-drying apparatus at an inlet temperature of 50 °C at a rotary disk rotation rate of 10,000 rpm, to give about 950 g of a 30 % erythromycin composition. Then, 70 g of magnesium oxide and 597 g of crystalline cellulose were added to, and homogeneously mixture was subjected to fluidized granulation in the presence of water as a granulating solvent to give a composition containing 10 % of erythromycin.

(Test method)

One gram of each of the test compositions was orally

administered to 10 healthy adults to evaluate was conducted on the basis of the following six ratings immediately after administration until 10 minutes passed.

- 0: Taste no bitterness
- 1: Taste a presence of bitterness
- 2: Taste bitter to some extent
- 3: Taste bitter
- 4: Taste bitter, but tolerable
- 5: Taste bitter intolerably

(Results)

The evaluation results on each test compositions by the ten adults were averaged, and Tables 1 and 2 show the results.

Table 1

	Im'ly after	1 minute	2 minutes	4 minutes	6 minutes	8 minutes	10 minutes
CnEx. 1	2	3	3	3	3	3	3
CnEx. 2	2	3	4	3	3	3	3
CnEx. 3	2	2	2	3	3	2	2
CnEx. 4	1	2	2	2	2	2	2
CnEx. 5	1	1	2	2	2	2	2
CnEx. 6	0	0	0	0	0	0	0
Ex. 1	0	0	0	0	0	0	0
Ex. 2	0	0	0	0	0	0	0
Ex. 3	0	0	0	0	0	0	0
Ex. 4	0	0	0	0	0	0	0
Ex. 5	0	0	0	0	0	0	0
Ex. 6	0	0	0	0	0	0	0
Ex. 7	0	0	0	0	0	0	0

CnEx. = Control Example, Ex. = Example

- 22 -

Table 2

	Im'ly after	1 minute	2 minutes	4 minutes	6 minutes	8 minutes	10 minutes
CnEx. 7	2	3	3	3	3	3	3
CnEx. 8	2	3	4	3	3	3	3
CnEx. 9	2	2	2	3	3	2	2
CnEx. 10	1	2	2	2	2	2	2
Ex. 8	0	0	0	0	0	0	0
Ex. 9	0	0	0	0	0	0	0
Ex. 10	0	0	0	0	0	0	0
Ex. 11	0	0	0	0	0	0	0
Ex. 12	0	0	0	0	0	0	0
Ex. 13	0	0	0	0	0	0	0

CnEx. = Control Example, Ex. = Example

## Test Example 3

## (Test Compositions)

Compositions for preparations, prepared in Examples 1 to 7.

Compositions prepared in Control Example 1 in Text Example 2.

## (Test method)

One gram of each of the test compositions was subjected to an elution test according to Japanese Pharmacopoeia, 11th edition.

An acetic acid buffer solution having pH of 4.0 was used as an eluting solution. The paddle rotation rate was set at 100 rpm, and the test compositions were measured for elutions ratios after 10 minutes.

## (Results)

Table 3 shows the elutions ratios.

Table 3

10 minutes	
Control Example 1	5
Example 1	100
Example 2	100
Example 3	100
Example 4	100
Example 5	100
Example 6	100
Example 7	100

## Test Example 4

(Test compositions)

Compositions for preparations, prepared in Examples 1 to 7.

Compositions prepared in Control Examples 3 to 6 in Test Example 2.

(Test method)

One gram of each of the above test compositions was separately suspended in about 5 ml, and the resultant suspensions were stored in a refrigerator (5 °C) for 1 day. Then, each of the suspensions was administered to ten healthy adults to evaluate the bitterness of the compositions. The evaluation was conducted on the basis of the following six ratings immediately after administration until 10 minutes passed.

0: Taste no bitterness

1: Taste a presence of bitterness

2: Taste bitter to some extent

3: Taste bitter

4: Taste bitter, but tolerable

5: Taste bitter intolerably

(Results)

The evaluation results on each test composition by the ten adults were averaged, and Table 4 shows the results.

Table 4

	Im'ly after	1 minute	2 minutes	4 minutes	6 minutes	8 minutes	10 minutes
CnEx. 3	4	4	5	5	5	5	5
CnEx. 4	3	4	4	5	5	4	4
CnEx. 5	3	3	3	4	4	3	3
CnEx. 6	0	0	0	0	0	0	0
Ex. 1	0	0	0	0	0	0	0
Ex. 2	0	0	0	0	0	0	0
Ex. 3	0	0	0	0	0	0	0
Ex. 4	0	0	0	0	0	0	0
Ex. 5	0	0	0	0	0	0	0
Ex. 6	0	0	0	0	0	0	0
Ex. 7	0	0	0	0	0	0	0

CnEx. = Control Example, Ex. = Example

### Test Example 5

(Test compositions)

Composition for preparations, prepared in Example 3.

Composition prepared in Control Example 6 in Test Example 2.

(Test method)

Two grams of the composition prepared in Example 3 and the composition prepared in Control Example 6 were

administered to six healthy adults according to a crossover method, and they were measured for concentrations in the blood to determine AUC and Cmax. Table 5 shows the results.

Table 5

	AUC ( $\mu$ g·hr/ml)	Cmax ( $\mu$ g/ml)
Example 3	8	1.3
Control Example 6	4	0.5

#### BRIEF DESCRIPTION OF DRAWINGS

Fig.1 is a graph showing the evalution results on each test composition until ten minutes passed.

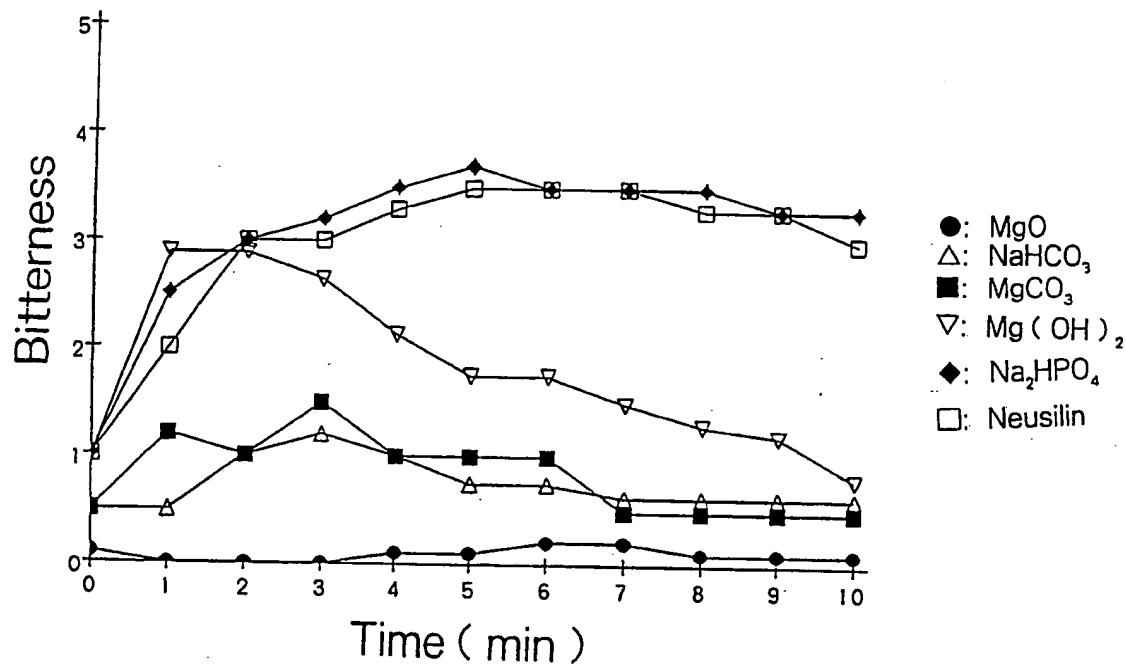
The total number of the points assaigned by the judges was divided by the number of ten adults to obtain the bitter taste raiting.

## CLAIMS

1. A composition for oral preparations, which comprises a complex formed by dispersing or dissolving an unpleasantly tasting basic drug and a functional polymer compound in a substance having a low melting point, 10 to 70 % by weight, based on the composition, of sugaralcohol and 0.1 to 7 % by weight, based on the composition, of basic oxide.
2. A composition according to claim 1, wherein the complex is a product obtained by melt- or heat-granulating a functional polymer compound dispersed or dissolved in a heat-melted substance having a low melting point and a basic drug.
3. A composition according to claim 1, wherein the functional polymer compound is contained in an amount of 1 to 60 % by weight based on the complex.
4. A composition according to claim 1, wherein the basic drug is one of unpleasantly tasting macrolides.
5. A composition according to claim 1, wherein the functional polymer compound is at least one selected from Eudragit® E and AEA.
6. A composition according to claim 1, wherein the substance having a low melting point is a pharmaceutically acceptable substance having a melting point of 40 to 120 °C and being insoluble or sparingly soluble in water.
7. A composition according to claim 1, wherein the basic oxide is magnesium oxide.
8. A composition according to claim 1, which has a form of dry syrup.

1/1

Figure 1



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 93/00291

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 A61K9/16; A61K9/00

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.C1. 5	A61K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y	DATABASE WPIL Week 9101, Derwent Publications Ltd., London, GB; AN 91-003127 & JP,A,2 279 622 (TAISHO PHARMACEUTICAL KK) 15 November 1990 see abstract --- US,A,3 857 939 (GREEN ET AL) 31 December 1974 see column 5 - column 6; example 3 --- US,A,3 627 885 (RONDELET ET AL.) 14 December 1971 see column 1, line 50 - line 69 see column 2, line 60 - line 63 see column 6; example 8 ---	1-8
Y		1-8
A		1,7

<sup>10</sup> Special categories of cited documents :<sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- "Z" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

02 JUNE 1993

Date of Mailing of this International Search Report

16. 06. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

BENZ K.F.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	<p>DATABASE WPI  Week 7544,  Derwent Publications Ltd., London, GB;  AN 75-72937  &amp; JP,A,49 081 526 (TOYO BREWING KK) 6  August 1974  cited in the application  see abstract</p> <p>---</p>	1-6
A	<p>EP,A,0 420 992 (TAISHO PHARMACEUTICAL CO.  LTD)  10 April 1991  see page 4; example 4  see page 4, line 50 - page 5, line 25</p> <p>---</p>	1-6,8
A	<p>EP,A,0 069 097 (ASTRA LÄKEMEDEL  AKTIEBOLAG)  5 January 1983  &amp; US,A,4 656 027  cited in the application</p> <p>---</p>	
A	<p>GB,A,2 122 490 (ASTRA LÄKEMEDEL  AKTIEBOLAG)  18 January 1984  &amp; US,A,4 994 260  cited in the application</p> <p>-----</p>	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

JP 9300291  
SA 70955

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 02/06/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-3857939	31-12-74	None		
US-A-3627885	14-12-71	None		
EP-A-0420992	10-04-91	CA-A- 2031206 WO-A- 9012566	19-10-90 01-11-90	
EP-A-0069097	05-01-83	CA-A- 1208559 JP-B- 4060968 JP-A- 58004714 SE-A- 8103843 US-A- 4656027	29-07-86 29-09-92 11-01-83 19-12-82 07-04-87	
GB-A-2122490	18-01-84	AU-B- 561954 AU-A- 1594383 CA-A- 1214726 EP-A, B 0101418 JP-A- 59016822 SU-A- 1722207 US-A- 4994260	21-05-87 05-01-84 02-12-86 22-02-84 28-01-84 23-03-92 19-02-91	